

REMARKS

I. Status of Claims:

Upon entry of the present amendment, claims 1, 13-21, and 24-36 will be pending in this application, claims 2-5, 7 and 9-12 having been previously canceled, claims 6, 8, 22, and 23 presently canceled, and claims 33-36 newly added. Claims 13-21 were withdrawn as drawn to a non-elected invention. Support for new claims 33 and 34 can be found, for example, at page 15, lines 22-23; and page 24, line 26, to page 25, line 5, of the application as filed. Support for new claims 35 and 36 can be found, for example, at page 23, lines 15-20, of the application as filed. Claims 1 and 24-28 have been amended herein. Support for the amendments can be found, for example, at page 4, lines 8-19; page 6, line 26, to page 7, line 8; page 11, lines 9-14; page 12, lines 12-35; page 15, lines 18-30; and Example 2. No new matter is added.

II. Rejections Under 35 U.S.C. § 103(a):

Claims 1, 6, 8, and 22-32 remain rejected as allegedly being obvious over Ridgway *et al.* (*Protein Engineering*, 9:617-621 (1996)) (“Ridgway”) in view of Peipp *et al.* (*Biochemical Society Transactions*, 30:507-511 (2002)) (“Peipp”) and Shalaby *et al.* (*Journal of Experimental Medicine*, 175:217-225 (1992)) (“Shalaby”). *See*, Office Action at pages 3-8. Claims 6, 8, 22, and 23 are presently canceled, so the rejection is moot as to them. With respect to the remaining claims subject to this rejection, Applicants traverse.

According to MPEP § 2142, the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. When determining whether a claim is obvious, an Examiner must make “a searching comparison of the claimed invention – including all its limitations – with the teachings of the prior art.” *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. Yieldup Int’l. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)) (emphasis added). Moreover, as the Supreme Court stated, “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness” and, “[t]o facilitate review, this [obviousness] analysis should

be made explicit.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). As explained in detail below, Applicants respectfully submit that the Patent Office has, again, not set forth a proper *prima facie* case of obviousness.

Applicants’ invention provides a novel method of producing a desired bispecific antibody following expression of all four chains of the antibody in a single cell. To solve the problem of random mispairing of the two heavy and two light chains of the bispecific antibody into 10 different arrangements, Applicants’ method involves inducing expression of the two chains of one arm of the bispecific antibody, ceasing induction of expression of the two chains of the first arm, and then inducing expression of the two chains of the second arm. When the heavy and light chains of the first arm are expressed in the cell, they will pair up together, because there is only one kind of light chain and one kind of heavy chain present in the cell and available for pairing. After induction of expression of those two chains ceases, most if not all of the expressed chains of the first arm will be paired up and unavailable for pairing with any subsequently expressed chains. At that point, expression of the heavy and light chains of the second arm is induced. When the heavy and light chains of the second arm are expressed, they pair with each other because there are no, or at least relatively few, heavy and light chains of the first arm available for pairing. Thus, regulating the timing of expression of the chains of the first and second arms solves the problem of random mispairing of the two heavy and two light chains of the bispecific antibody into 10 different arrangements. The first and second arms of the bispecific antibody can then be heterodimerized using any technique known in the art (*e.g.*, “knobs-into-holes” engineering). None of the cited references either alone or in combination suggests Applicants’ claimed invention.

Ridgway teaches the use of “knobs-into-holes” engineering of antibody C_H3 domains for heterodimerization of heavy chains. Ridgway’s experiments were conducted using the heavy and light chains of anti-CD3 and an immunoadhesin, CD4-IgG, which is a recombinant fusion of soluble CD4 and the Fc portion of immunoglobulin G (*i.e.*, a portion of a heavy chain). Ridgway engineered a “knob” in the C_H3 domain of CD4-IgG by replacement of threonine 366 with a tyrosine. The “knob” was designed to insert into a “hole” in the C_H3 domain of a humanized anti-CD3 antibody created by replacing the tyrosine at position 407 with a threonine. Ridgway coexpressed these proteins by co-transfecting phagemids encoding one anti-CD3 heavy chain,

one anti-CD3 light chain and a CD4-IgG fusion polypeptide into cells to produce heterodimers, each of which had three chains: one antibody heavy chain, one antibody light chain, and one CD4-IgG chain. Ridgway reports that the anti-CD3/CD4-IgG hybrid represented up to 92% of the purified protein pool following co-expression of the “knob” and “hole” containing C_H3 domains, whereas the anti-CD3/CD4-IgG hybrid represented only 57% of the protein purified when wild type CH3 domains were used. Thus, Ridgway’s experiments show that knobs-into-holes engineering of C_H3 domains can be useful in controlling heterodimerization of Fc regions. Applicants emphasize that Ridgway’s method does not solve the mispairing problem with respect to the light chains, which lack an Fc region. Nowhere in Ridgway is there any suggestion of inducing expression of the first light and heavy chains and following expression of the first light and heavy chains, causing induction of expression of these chains to cease, and subsequently inducing expression of the second light and second heavy chains. Instead, Ridgway teaches coexpression of the CD3 antibody heavy and light chain and the immunoadhesin (CD4-IgG) (*see*, page 617, right column, second full paragraph; and page 618, left column, “*Expression and purification of Ab/IA variants*”).

Shalaby teaches the production of a bispecific F(ab')₂ consisting of an arm that has specificity toward the extracellular domain of p185^{HER2} and an arm that has specificity toward the human T cell surface marker CD3. Shalaby avoids the mispairing of the four chains of the bispecific F(ab')₂ by expressing each arm separately, in different cultures of cells, followed by purification of each arm from the cells in which it was expressed, chemical modification of one of the arms to make it reactive, followed by directed chemical coupling of the two arms to each other (*see*, page 218, left column, first full paragraph and the carryover paragraph of pages 218-219). Nowhere in Shalaby is there any teaching, suggestion or motivation to express all four chains of the bispecific antibody in the same cell. Thus, it should not be surprising that there is no suggestion whatsoever in Shalaby of inducing expression of the first light and heavy chains and, following expression of the first light and heavy chains, causing induction of expression of these chains to cease, and subsequently inducing expression of the second light and second heavy chains.

Peipp is a review article that discusses bispecific antibodies. Figure 1 of Peipp provides, *inter alia*, a schematic representation of a bispecific antibody format that is referred to as “knobs-

into-holes.” Although this diagram shows a bispecific antibody having two different arms, Applicants note that this diagram must be considered in the context of Peipp’s disclosure. Outside this figure, the only other mention of knobs-into holes is the following brief description of a technology described in a review article by Paul Carter (*J. Immunol. Methods*, 248:7-15 (2001)): “Furthermore, Paul Carter described an elegant technology which even allowed generation of ‘full-size’ recombinant bispecific antibodies. Here, heterodimerization of two different heavy chains is enforced by ‘knobs-into-holes’ technology, which ultimately leads to a bispecific IgG molecule” (*see*, page 510, left column, first incomplete paragraph). The method described in Carter uses the knobs-into-holes engineering to create heavy chain heterodimers and the “L chain mispairing problem was circumvented entirely by constructing a BsIgG from antibodies that utilize identical L chains.” (*see*, Carter, page 9, left column, carryover paragraph; Fig. 1, especially Fig. 1C; emphasis added). Thus, considered in context, Peipp’s knobs-into-holes bispecific antibody in Figure 1 actually corresponds to Carter’s knobs-into-holes heavy chains paired with identical light chains. No other way to produce knobs-into-holes bispecific antibodies with proper heavy-light chain pairing is suggested in Peipp or Carter. Nowhere in Peipp or Carter is there any teaching or motivation whatsoever of Applicants’ claimed method.

The combined teachings of Ridgway, Shalaby, and Peipp fail to suggest inducing expression of the first light and heavy chains and following expression of the first light and heavy chains, causing induction of expression of the first light and heavy chains to cease, and subsequently inducing expression of the second light and second heavy chains, as required by Applicants’ claims. This is understandable because Ridgway, Shalaby and Peipp provide completely different approaches from Applicants’ approach for dealing with the light chain mispairing problem: Ridgway does not use a second heavy-light chain pair, but instead uses an immunoadhesin chimeric polypeptide; Shalaby expresses both arms of the bispecific antibody in different cells and couples them after the two chains of each arm have paired; and Peipp uses two identical light chains. None of these references even hints at the solution provided by Applicants: expressing the H and L chains of the two arms of the antibody at different times using means that allow regulated expression. It is well settled that the “Patent and Trademark Office (PTO) must consider all claim limitations when determining patentability of an invention over the prior art.” *In re Lowry*, 32 F.3d 1579, 1582 (Fed. Cir. 1994). The Examiner has not

provided a reason one of ordinary skill, upon reading the cited references, might have wanted to express the two arms of a bispecific antibody at separate times, much less established that it would have been obvious to do so. At least because the combined references fail to teach claim limitations of Applicants' independent claims, the examiner has failed to set forth a *prima facie* case of obviousness.

Response to Examiner's Comments

As a preliminary matter, it is noted that page 5 of the Office Action states that "Applicants allegations on pp. 8-13 of the Response of 2/16/10 have been considered and are found persuasive." In view of the Examiner's subsequent remarks, that quote from the Office Action appears to misstate the Examiner's actual views. Clarification is respectfully requested.

The Examiner first takes issue with the following paragraph bridging pages 11-12 of the response filed February 16, 2010:

Ridgway was able to create heterodimers by the "knobs-into-holes" engineering design strategy, and predicted that this technique, if applied to bispecific antibodies, would reduce the number of random mispairings that occur in the cell from "10 major species down to four or less." Ridgway's reference to "four or less" species reflects his recognition that the problem of mispairing of a light chain with the incorrect heavy chain is not solved by the knobs-into-holes technique. Ridgway simply avoided this problem in his own experiments by using only one kind of light chain and one kind of heavy chain, and having the CD4 IgG fusion polypeptide serve as the second arm.

First, the Examiner states that Applicants' "conjecture" about what Ridgway was contemplating by using only one kind of light chain and one kind of heavy chain is "unsubstantiated by extrinsic evidence" (see, Office Action, page 6, first full paragraph). In response, Applicants note that Ridgway was fully aware of the light chain mispairing problem, as this reference states, in relevant part, "In addition, the mutations identified are anticipated to increase the clinical potential of Fc-containing BsAb by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less" (page 620, right column, fourth full paragraph). The ordinary artisan would understand this statement to mean that Ridgway recognized that bispecific antibodies can pair up incorrectly, i.e., the heavy chain of one arm of the bispecific antibody may pair up with itself rather than the heavy chain of the second arm and the light chain of one arm may pair up incorrectly with the heavy chain of the other arm. Ridgway is focused entirely on how to ensure the correct pairing of heavy chains

using the knobs-into holes technique. However, heterodimerization of the Fc domains using the knobs-into-holes technique does not solve the light chain mispairing problem. Furthermore, Ridgway provides no solution to the light chain mispairing problem. Thus, the ordinary artisan reading Ridgway would understand that Ridgway focused on one part of the immunoglobulin mispairing problem (the heavy chain-heavy chain mispairing problem) without the complicating influence of using two different light chains.

Second, the Examiner alleges that

Applicants fail to recognize that Ridgway [*sic*] appreciates using the knobs-into-holes techniques for pairing bi-specific Fc-containing antibodies when the range limitation “four *or less*” reads on no mispairings. In other words, Ridgway [*sic*] recognizes the existence of experimental error along with the possibility of achieving fully matched antibody pairings with no error.” (*see*, Office Action, page 6, second full paragraph).

In response, Applicants note that Ridgway addresses itself solely to heavy chain pairing. Mispairing of the light chain is avoided in Ridgway by using a single light chain and an immunoadhesin instead of a second antibody arm, allowing Ridgway to use a single light chain that necessarily pairs with the only heavy chain present to form the first antibody arm. There is simply no teaching or suggestion in Ridgway of how to avoid light chain mispairing. The knobs-into-holes method described in Ridgway is entirely directed to heterodimerization of a “knob-containing” Fc region with a “hole-containing” Fc region. As the Examiner is fully aware, Fc regions are found in heavy chains, not light chains. There is no teaching of any sort in Ridgway of circumventing mispairing of antibody light chains in this reference. Thus, Ridgway is wholly deficient when it comes to teaching three or fewer mispaired antibody species, let alone zero mispairing when two different light chains and two different heavy chains are used. Without a solution provided by Ridgway to the light chain mispairing problem, the phrase “four or less” simply cannot be read as Ridgway’s teaching or suggesting how to achieve “fully matched antibody pairings with no error.”

Third, the Examiner purports that

Ridgway [*sic*] provides at the very least a scintilla of evidence needed to establish a prima facie motivation to try using the knobs-into-holes technique in the same cell expressing different Fc-containing antibodies. It is the examiner’s position that it would have been obvious to try using the knobs-into-holes technique for making bispecific antibodies in the same cell where as in the present case the ordinary artisan would have chosen ‘from a finite number of identified, predictable solutions, with a reasonable expectation of success’” (*see*, Office Action, page 7, first paragraph).

Applicants agree that Ridgway teaches a way to avoid the mispairing of heavy chains by using the knobs-into-holes technique in the Fc region. However, there is simply nothing in Ridgway that solves the light chain mispairing problem. Given this fact, the ordinary artisan would not consider it obvious to try “using the knobs-into-holes technique for making bispecific antibodies in the same cell” because it would still leave one with the light chain mispairing problem. Instead, the ordinary artisan would have chosen “from a finite number of identified, predictable solutions, with a reasonable expectation of success”, i.e., from the solutions presented by Ridgway (use of an immunoadhesin instead of a second heavy chain and second light chain), or Shalaby (preparing the two antibody arms in separate cells and then coupling them together by chemical means), or Peipp/Carter (using the same light chain for both arms). Nowhere in the Office Action has the Examiner provided any evidence that temporal expression of the two arms of the bispecific antibody was an “identified, predictable solution[s], with a reasonable expectation of success” to the light chain mispairing problem.

The Examiner next focused on the following arguments made by Applicants in the response filed February 16, 2010:

Rather than teaching a temporally separated expression of the two arms in order to control proper pairing of light and heavy chains, the approaches taught in the cited art to overcome the mispairing of the light and heavy chains include:

- (1) using a single, Fc-containing fusion polypeptide (CD4-IgG) as the second arm instead of using a heavy chain associated with a light chain as the second arm (Ridgway);
- (2) expressing the antigen binding fragments (Fab') of two different antibodies in separate cells and chemically coupling the purified Fab' fragments to form a heterodimer (Shalaby); and
- (3) using identical light chains (Peipp/Carter).

The Examiner states

it is noted that the features upon which Applicant relies (i.e., a temporally separated expression of the two arms in order to control proper pairing of light and heavy chains) are not recited in the rejected claim(s)” and that “[h]ere the claims merely recite the cessation of the expression of the first antibody is overlapping with inducing expression of the second antibody. There is no clear division or distinction between steps c) and d) of Claims 1 and 28 where expression of the first antibody is fully inhibited before induction of the second antibody” (see, Office Action, paragraph bridging pages 7-8).

Applicants confess to being bewildered by the Examiner’s interpretation of the relevant claim language. The claim language at issue recites: “(c) causing induction of expression of the first

light chain and first heavy chain to cease; (d) subsequent to step (c), inducing expression of the second light chain and second heavy chain in the cell” (emphasis supplied). Contrary to the Examiner’s assertion, the claims do not recite that cessation of expression of the first antibody is “overlapping” with inducing expression of the second. In fact, they recite the opposite: that expression of the second light and heavy chains is induced subsequent to the cessation specified in step (c). “Subsequent” means “after,” not “overlapping.” In case the Examiner continues to believe that “subsequent” means “overlapping,” Applicants have added essentially redundant language “such that expression of the first light chain and first heavy chain is temporally separate from expression of the second light chain and second heavy chain in the cell” to claims 1 and 28.

For at least the foregoing reasons, Applicants respectfully assert that the Patent Office has not established a *prima facie* case of obviousness and therefore request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement:

Claims 1, 6, 8, and 22-32 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office Action alleges that “the specification does not reasonably provide enablement for inducing just any kind of recombinant cell to express a first light chain and a first heavy chain at one time and to express a second light chain and a second heavy chain *at a different time under just any conditions.*” See, Office Action at pages 8-13; emphasis in original.

The Examiner alleges that

in order to obtain two different functional antibodies being expressed in and by the very same eukaryotic cell, it is not sufficient to perform step c) in Claims 1 and 28 (where the expression of the first antibody chains are ceased) before performing step d) (where the expression of the second antibody chains are induced). For the generic method to meet the enablement requirement, expression of the second antibody must be under the control of different inducing elements that are separate and distinct from the inducing elements of the first antibody (see, Office Action, page 12, first full paragraph).

Without acquiescing to this rejection, and solely to expedite prosecution of this case, Applicants have amended independent claims 1 and 28 to recite, in relevant part, that “the expression of the first light chain and the first heavy chain is induced by a first exogenous expression regulator, expression of the second light chain and the second heavy chain is induced by a second exogenous expression regulator, and the first and the second exogenous expression regulators are different.” Applicants respectfully submit that these amendments are sufficient to overcome the

outstanding enablement rejection with respect to the regulation of expression of the first and second antibodies.

The Examiner also alleges with respect to claim 8 that the ordinary artisan would need to engage in undue trial and error experimentation to identify “where within the antibody structure, the knobs-to-holes mutation should be introduced,” and with respect to claim 23, “where the first and/or second heavy chains contain mutations that promote formation of multimers” (see, Office Action, paragraph bridging pages 12-13). Applicants first note that claim 23 has been canceled in the present Amendment; thus, this rejection is moot as to claim 23. Applicants respectfully disagree with Examiner regarding claim 8 (the limitations of which are now included in claims 1 and 28). The “knobs-into-holes” technique was well known at the time of the filing of the present application, as evidenced by the Examiner-cited references Ridgway and Peipp. In addition, the review article by Carter also supports the knowledge of this technique by the ordinary skilled artisan (see, pages 9-10 and Fig. 2). Furthermore, the application as filed provides more than sufficient guidance to use the claimed invention (see, e.g., paragraph bridging pages 10-11; and Example 1).

The Examiner also alleges that

the ordinary artisan would be required to perform undue trial and error experimentation to test various different compounds for expression regulating effects on the endogenous promoters for the first light and heavy chain, and different compounds for expression regulating effects on the endogenous promoters for the second light and heavy chain, especially where the compound-inducible expression regulation is required to be performed in the same cell to differentially express the different light/heavy chain pairs (see, Office Action, page 13, first full paragraph).

In response, Applicants note that none of the pending claims refers to “endogenous promoters,” even prior to the present amendment. Instead, the recombinant cell used in claim 1¹ comprises

exogenous DNA encoding a first light chain and a first heavy chain and exogenous DNA encoding a second light chain and a second heavy chain, . . . wherein the expression of the first light chain and the first heavy chain is induced by a first exogenous expression regulator, expression of the second light chain and the second heavy chain is induced by a second exogenous expression regulator, and the first and the second exogenous expression regulators are different.

Guidance regarding different expression regulators that can be used in the claimed invention is provided, e.g., at page 12, lines 23-35; page 15, lines 18-30; and page 25, lines 7-19 of the specification as filed. In view of this disclosure as well as the state of the art at the priority date

¹ Claim 28 uses the term “nucleic acid” instead of “DNA.”

of this application, Applicants respectfully submit that the specification reasonably enables the identification of expression regulators for use in the claimed methods. It is noted that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463 (Fed. Cir. 1984).

Finally, the Examiner purports that the

ordinary artisan would be required to perform undue trial and error experimentation in order to construct a poly-cistronic vector enabled to express in a different time frame the first antibody pair and then the second antibody pair and all occurring within the same cell, because no guidance is provided in the original specification as filed for the starting materials and/or the generation of any such vector construct (see, Office Action, page 13, second full paragraph).

This rejection appears to be directed at claim 26. In view of the skill in the art of molecular biology at the time of the priority date of the present application, the teachings of the application as filed (e.g., page 13, line 14 to page 15, line 17), and the teachings of the prior art regarding dicistronic vectors (see, e.g. Shalaby, page 218, right column, "*Fab Fragment Expression for humAb4D5-8 and Anti-CD3 mAb Variants*"), there would appear to be no reason for Applicants to provide detailed guidance in the specification regarding the generation of a polycistronic vector. The Examiner is reminded that the specification is addressed to a person of skill in the art. If the Examiner intends to maintain this ground of rejection, she is respectfully asked to explain why she believes constructing the desired polycistronic vector would require "undue experimentation" by a molecular biologist of ordinary skill in the art of constructing of polycistronic vectors, given the teachings in the specification and the state of the art at the priority date of this application.

In view of the foregoing remarks, Applicants request that this rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Applicant : Taro Miyazaki et al.
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CONCLUSION

As all grounds for rejection are believed to have been overcome, Applicants ask that the claims be allowed and that a Notice of Allowability be issued. If any issues remain, the Examiner is invited to telephone the undersigned at the telephone number provided below to discuss them.

Applicants petition for a five-month extension of time to respond to the outstanding Office Action. Please apply any required charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0154US1.

Respectfully submitted,

Date: July 5, 2011

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